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Final Report

APP-Induced Gene Transcription: Role in Alzheimer's Disease

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Background

Beta-amyloid, the protein fragment that is a prime suspect in Alzheimer's disease, is clipped off a longer protein called amyloid precursor protein (APP). APP is a transmembrane protein, which means it has portions residing both inside and outside a nerve cell. Beta-amyloid fragments appear to accumulate outside of cells, where they aggregate into the plaques that are a hallmark of Alzheimer pathology.

Researchers have only recently begun to investigate the portion of APP that remains inside the cell and to assess its potential role in Alzheimer's disease. This internal portion of APP, termed the APP intracellular domain (AICD), appears to travel from the outer membrane toward the center of the cell. Many researchers believe that AICD may play a key role in activating certain genes, so that the cell begins producing the proteins whose "blueprint" the genes encode. But it is not yet known which genes AICD might activate or whether such activation may contribute to Alzheimer pathology.

Goal of study

Edward H. Koo, M.D., and colleagues have teamed up with the company Genpathway, Inc., to identify genes and proteins that interact with AICD. In some cases, this research will involve following up on previously identified suspects. In other cases, Koo and his team will use a variety of molecular biology techniques, along with Genpathway's proprietary technology, to identify new genes and proteins that interact with AICD.

Research outcomes

To conduct this one-year pilot study, the research team used brains of genetically altered mice that overexpress APP, along with brains of normal mice. The investigators began their survey by looking for "gene tags," or small segments of genes, that are bound to AICD. Koo and his team identified 1,000 tags of particular interest and began the process of sequencing, or translating the genetic code, of these tags.

Future work

Dr. Koo's team will repeat these studies to validate their findings. If they are satisfied that these are bona fide APP target genes, they will begin work to identify the biological relevance of these genes and their protein products and to determine whether their activation plays any role in Alzheimer's disease.

Approved by William H. Thies, Ph.D., vice president of Medical and Scientific Affairs, as a confidential communication to the Judy Gelfand Fund. Alzheimer's Association grant IIRG-03-6374 final report.